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Developing Better Economic Models of Osteoporosis: Considerations for the Calculation of the Relative Risk of Fracture

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ABSTRACT

Objective: Simulation models are often used to assess cost-effectiveness of osteoporosis therapies. Many cost-effectiveness analyses are interested in a subset of the general population, such as high-risk patients. As the analyses are very sensitive to the assumed risk of fracture, it is imperative that the rates accurately reflect the fracture risk in the specified target population. The objective of this study was to describe the methodological difficulties and present some possible solutions for calculating the risk of facture in target populations of interest.

Methods: For binary risk factors, a method for converting from a relative risk (RR) for people with a risk factor relative to those without, to an RR in the target population compared with the general population, is described. For continuous risk factors (i.e., bone mineral density [BMD]), data are often provided as an RR of fracture per SD decrease. A method for converting from an RR per SD decrease to an RR in those below a certain BMD threshold, compared with the general population, is presented.

Results: These results should allow future economic models to more accurately incorporate existing knowledge of risk factors by introducing methods to calculate fracture risk estimates in a target population.

Conclusion: It illustrates the importance of considering the prevalence of risk factors in the general population when calculating RR in a target population.

Keywords: cost-effectiveness analysis; osteoporosis; relative risk; risk factors.

Introduction

Over the last decade, our knowledge of risk factors for osteoporotic fractures has greatly increased. Not coincidentally, these years have seen the development of several new therapies that effectively decrease fracture risk. With the development of new drug therapies came the need to assess their economic value to inform health-care budget allocation decisions. Many cost-effectiveness analyses to date have utilized disease simulation models to capture the long-term impact of osteoporosis therapies, which can have economic and clinical benefits that extend beyond the time horizon of most clinical trials [1–6]. These analyses are very sensitive to the assumed fracture risk in the target population, with cost-effectiveness ratios decreasing when fracture risk rises.

In many analyses, the target population is a subgroup of the general population, commonly, high-risk patients who are at greatest need for treatment. For example, one may want to consider for treatment osteoporosis patients with the following risk factors: very low bone mineral density (BMD), a previous vertebral fracture, and a history of falls. Absolute fracture rates in such high-risk groups are typically not known. Instead, the fracture rate must be calculated based on the general population fracture rate and the increased risk of fracture associated with each risk factor. This is normally carried out by multiplying the general population fracture rate by an overall relative risk (RR) that represents the risk of fracture in the target population versus the general population. Nevertheless, the RR estimates available in the literature are commonly for patients with a risk factor compared with those without. Given that cost-effectiveness analyses seek to estimate the value of treating an at-risk population compared with doing nothing, the risk comparison of interest is between the target population and the general population. For this application, the published RRs are an overestimate because some patients within the general population will also have the risk factor.

In many analyses, the explicit calculation of RR for the target population is not conducted, or the risks are overestimated. The purpose of this article is to describe the challenges in determining RR in a target population and present some possible approaches. Specifi-

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cally, we will address two issues: 1) a method for converting RR estimates for binary risk factors (e.g., history of fracture); and 2) a method for converting RR estimates for continuous risk factors (e.g., BMD).

Methods

Before addressing the specific issues with binary and continuous risk factors, it is necessary to understand how RRs are typically used. In general, several steps are required if one wants to calculate fracture rates in the target population based on the presence of risk factors.

The risk of fracture in the target population is calculated by multiplying the fracture incidence rate for the general population, by an overall RR estimate that is indicative of the risk in the defined target population versus the risk in the general population (e.g., fracture rate × overall $RR_{tp/gp}$). The overall $RR_{tp/gp}$ often reflects a range of both binary (i.e., previous vertebral fracture, history of fracture since age 50 years, maternal history of hip fracture) and continuous (i.e., BMD, age) risk factors in the target population.

The overall RR (overall $RR_{tp/gp}$) is the product of the RR associated with each individual risk factor in the target population. For example, the $RR_{tp/gp}$ for a population with a BMD T-score of –2.5 and a previous vertebral fracture is the RR due to the low BMD T-score multiplied by the RR of a previous vertebral fracture. It should be noted that multiplying the individual RR estimates implies that the factors are independent. Because age, BMD, and other risk factors are closely related, it is important that one utilize data on RR from analyses that have simultaneously adjusted for all of the included risk factors. This was true of the data included in this analysis.

The methodological challenges discussed in the next sections arise while estimating the RR associated with each individual risk factor.

Binary Risk Factors

A number of important binary risk factors for hip fracture in postmenopausal women have been identified, including history of postmenopausal fracture, maternal history of hip fracture, and low body weight [4,6–9]. These risk factors remain important even after adjustment for each other as well as age and BMD. Table 1 shows, as examples, two of these risk factors, history of postmenopausal fracture and maternal history of fracture, together with their approximate RRs [4].

In the table, $RR_{w/wo}$ reflects the fracture risk in those people with the risk factor compared with those without. For example, women with a history of postmenopausal fracture are at double (RR = 2.0) the risk of a hip fracture than women who do not have a history of postmenopausal fracture. Nevertheless, it would be an overestimate of risk to apply this risk factor when comparing people with the risk factor with the general population because the general population will include both those with the risk factor and those without. The proportion of the general population with the given risk factor will vary according to their age, country, and other factors. Often, economic analyses of osteoporosis therapies do not take this into account. Either they use the RR without adjustment for prevalence in the general population or they do not explicitly calculate RR rates instead of using illustrative analyses that assume the target population is at two, three, or four times the risk of fracture.

The following formula can be used to adjust $RR_{w/wo}$ to better reflect the estimate of interest, which is the RR of those people with a risk factor compared with the general population ($RR_{w/gp}$) [10]. The magnitude of the correction depends on the prevalence of the risk factor:

$$RR_{w/gp} = RR_{w/wo} / [(p \times RR_{w/wo}) + (1 - p)] \quad (1)$$

where p is the prevalence of the risk factor in the population being studied.

The last set of columns in Table 1 show that the $RR_{w/wo}$ is attenuated after the correction for prevalence and that this attenuation increases with prevalence. For example, the $RR_{w/wo}$ for history of postmenopausal fracture is 2.0, comparing those with the risk factor to those without the risk factor before correction, but shrinks to 1.74 when the prevalence is 15% and to 1.54 when the prevalence is 30%.

Figure 1 shows the attenuation in $RR_{w/wo}$ as a function of the RR and prevalence. At the same prevalence, the absolute magnitude of attenuation is greater as the RR increases. For a risk factor with 50% prevalence, for example, if the $RR_{w/wo}$ is 3.0, the $RR_{w/gp}$ is reduced to about 1.5.

Table 1 Examples of risk factors for hip fracture and the effect of correction for prevalence

Risk factor	Type	Relative risk ($RR_{w/wo}$)	Unit	Prevalence of risk factor		Relative risk corrected for prevalence ($RR_{w/gp}$)	
				Age 65	Age 75	Age 65	Age 75
History of postmenopausal fracture	Binary	2.0	Yes/no	15%	30%	1.739	1.538
Maternal history of hip fracture	Binary	1.5	Yes/no	10%	14%	1.429	1.402
Femoral neck BMD	Continuous	2.3	Per SD	See Tables 2 and 3			

BMD, bone mineral density.

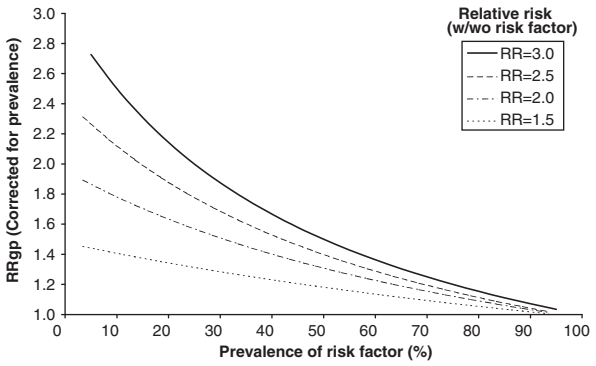

Figure 1 Relative risk (compared with general population [gp] risk) as a function of prevalence of a binary risk factor.

Continuous Risk Factors (i.e., BMD)

Often, when considering continuous risk factors, economic analyses focus on defining the target population based on whether they fall above, or below, a threshold level. For example, in osteoporosis, one might be interested in the risk of fracture among those with BMD values below a T-score of –2.5, the World Health Organization threshold definition of osteoporosis. Often, analyses in osteoporosis consider risk at the threshold rather than at or below the threshold, which is an underestimate of the true fracture risk because patients below the threshold will be at higher risk than those at the threshold. Our goal was to develop an algorithm for assessing the risk of fracture in a population below a threshold compared with the overall risk in the general population. To do this for a target population compared with the general population, two issues must be considered: determining the distribution of the target population below the threshold and adjusting for the proportion of the general population below that threshold. A similar methodology may be used for other continuous risk factors.

The following assumptions were made for BMD as a continuous risk factor:

1. BMD at any age follows a normal (Gaussian) distribution with a known mean and an SD [11]. For purposes of illustration, we will work with femoral neck BMD and use the distributions from the National Health and Nutrition Examination Survey III [11]. Table 2 shows the mean and SD for femoral neck BMD (using a Hologic, QDR 1000) among Caucasian women derived from the NHANES III study. It also shows the proportion below two T-score thresholds (–2.5 and –1.0) at ages 65 and 75 years using the NHANES III means, SD, and assumption of normal distribution.
2. The relationship between BMD and fracture risk follows a logistic risk function. The logistic function is commonly used to describe the relationship between risk factors and disease outcomes [12]. We have previously published methods for calculating parameters for a logistic distribution when both the RR per SD decrease (BMD to fracture) and the fracture incidence in the general population are known [13]. We will use the general population rates of hip fracture derived from the National Hospital Discharge Survey [14]. For purposes of illustration, it is assumed that the RR per SD relating femoral neck BMD to hip fracture risk is 2.3 [15].

Table 2 Distribution of BMD at the femoral neck at ages 65 and 75 years [10]

	Age 65	Age 75
Mean BMD (g/cm^2)	0.682	0.618
Standard deviation	0.114	0.099
Population below T = –1.0	69%	89%
Population below T = –2.5	18%	34%

BMD, bone mineral density.

Using the assumptions outlined in numbers 1 and 2, the risk of hip fracture among those with BMD values less than a threshold value BMD_T can be calculated using the following relationship:

$$\int_{-\infty}^{BMD_T} Pfa(\alpha_a\beta_a|BMD)N(\mu_a,\sigma_a)dBMD \qquad (2)$$

where

1. Pfa (α_a,β_a) is the 5-year probability of fracture at age *a* at a specific BMD value (assumed to be a logistic function), with β_a as the logistic slope relating BMD to fracture risk at age *a*, and α_a as an intercept term at age *a*.
2. $N(\mu_a,\sigma_a)$ is the Gaussian distribution function with μ_a being the mean of BMD at age *a* and σ_a being the SD of BMD at age *a*.

The functions and relationships outlined in 1) and 2) allow calculation of the general population risk of fracture at a particular age by integrating with T set at positive infinity if the two parameters of the normal distribution and the logistic function are known. Conversely, if the fracture risk in the general population at a particular BMD threshold is known, we can use it together with three of the four Gaussian/logistic parameters to solve for the fourth parameter. Specifically, we can use population age-specific hip fracture incidence data [14], the mean and SD of BMD at a specific age, and the odds ratio per SD for BMD (a function of the slope coefficient of the logistic function) to then solve for the intercept coefficient (α_a). Once estimates are available for the four parameters within the integral, the probability of hip fracture for a population with BMD values below any specific T-score threshold can be calculated.

For example, we can calculate the risk in those below the threshold for a set of T-score thresholds

Table 3 Risk of hip fracture as a function of BMD T-score

Age (year)	T-score threshold	Fracture risk* (gp) (%)	Proportion below threshold (%)	Risk at threshold		Risk below threshold	
				Risk (%)	RR compared with gp risk ($RR_{w/gp}$)	Risk (%)	RR compared with gp risk ($RR_{w/gp}$)
65	−1.0	1.30	69	0.55	0.423	1.60	1.231
	−2.0	1.30	33	1.30	1.000	2.50	1.923
	−2.5	1.30	18	1.90	1.462	3.20	2.462
	−3.0	1.30	8	3.00	2.308	4.30	3.308
	−3.5	1.30	3	4.40	3.385	6.00	4.615
75	−1.0	4.30	89	1.20	0.279	4.60	1.070
	−2.0	4.30	55	2.70	0.628	6.30	1.465
	−2.5	4.30	34	4.00	0.930	8.10	1.884
	−3.0	4.30	17	6.30	1.465	11.00	2.558
	−3.5	4.30	6	9.40	2.186	15.60	3.628

*General population (gp) fracture risk over 5 years.
BMD, bone mineral density; RR, relative risk.

from −1.0 to −3.5. Because the overall fracture risk in the general population is often known, we will focus on the ratio of the risk in those below the threshold compared with the general population.

The means and SDs in Table 2 will be used as the parameters for the normal distribution in the calculations. BMD decreases with age, for example, between ages 65 and 75 years it decreases approximately 10%, from 0.68 g/cm^2 to 0.62 g/cm^2. Using the specific means and the normal distribution, the proportions below each T-score threshold are also calculated. For example, the proportion of the population with BMD T-score below −2.5 increases from 18% at age 65 years to 34% at age 75 years.

Table 3 shows the risk of hip fracture in those below the T-score thresholds at age 65 and 75 years. At age 65 years, the 5-year risk of hip fracture in the general population is 1.3% [13]. The risk in those with BMD T-scores below −2.5 is 3.2%, yielding an RR of 2.46. The risk increases as more extreme thresholds are chosen. For example, in the 3% of 65-year-old women with BMD T-scores below −3.5, the risk is 6.0% while among the 69% with BMD T-scores below −1.0, the risk is only 1.6%. At the same T-score thresholds, the risk increases with age. For example, the risk in those with femoral neck BMD T-scores below −2.5 increases from 3.2% at age 65 years to 8.1% at age 75 years. Note that if one approximates the risk in those below the threshold using BMD at the threshold, the risk is significantly underestimated.

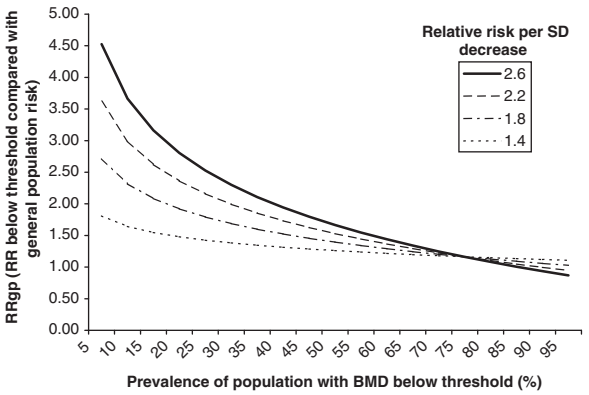

Figure 2 Relative risk of fracture (compared with general population [gp] risk) as a function of prevalence of population with bone mineral density (BMD) below a threshold.

Figure 2 shows the RR_{gp} as a function of the prevalence of the population with BMD below the threshold for a range of RRs per SD decrease (from 1.4 to 2.6), representing the range seen for commonly used BMD devices [4]. The RR_{gp} can be obtained for other RRs per SD decrease by interpolation from this figure.

Conclusions

Growth in available osteoporosis therapies has led to a need for tools to assist in the evaluation of new therapies for high-risk populations. Simulation models are well suited to such evaluations because they allow cost-effectiveness analyses in populations where prospective data are unavailable and collection of such is unrealistic [2,3]. Nevertheless, to accurately guide decision makers in the efficient allocation of resources, these models must utilize realistic data that reflect fracture risk in the target population. This article addressed calculation of RR for both dichotomous and continuous risk factors.

It is commonly referenced that women with a history of postmenopausal fracture are twice as likely to have a fracture as women without a similar history. However, cost-effectiveness analyses seek to compare treatment of high-risk populations with the general population, not with patients without risk factors. It is not commonly considered in analyses that for binary risk factors, the increased risk in those with the risk factor compared with average risk in the general population is much less than the increased risk compared with those without the risk factor. We have quantified the extent to which the attenuation depends on the prevalence of risk factors and have provided a nomogram that can be used to make that adjustment.

Similarly, while the relationship between BMD and hip fracture risk is often defined as the RR per SD decrease in BMD, the elevation in risk in the target population with low BMD compared with the general population depends not only on the RR per SD decrease, but also on the prevalence of low BMD. Similar to a previous study [16], we have shown that the practice of assigning risk in a population below a BMD threshold by assuming BMD exactly at the threshold generally will underestimate the true RR. We also illustrate the attenuation due to low BMD in the general population and have provided a figure that allows one to calculate the correct RR compared with the general population for commonly utilized RR per SD decreases.

When implementing the methods discussed, another key consideration is that age, BMD, and other risk factors are all closely related. As such, it is important that economic models considering these risk factors utilize data on RR from analyses that have simultaneously adjusted for all of the included risk factors. This imposes an important limitation on the variables that can be included in economic models because simultaneous consideration of all risk factors deemed important to an analysis is not common. For example, the Study of Osteoporotic Fractures (SOF) has provided an analysis of the risk factors for hip fracture which includes calcaneal BMD together with other risk factors [6] but has not published studies of these risk factors together with hip BMD, radial BMD, or calcaneal ultrasound. The Epidemiology of Osteoporosis Study also provides information about risk as related to femoral neck BMD in an elderly cohort (age >75 years), but it considers only a limited set of other risk factors [7]. This lack of data is even more acute when considering risk factors for types of fractures other than hip fractures. These data are especially important when calculating combined RRs for input into economic evaluations. The multiplicative approach (i.e., multiply individual adjusted RRs) assumes that risk factors are independent or that the RR has been adjusted for confounding effects (as is the case with the SOF data). It is important that those building economic models for osteoporosis recognize these limitations.

Overall, the methods discussed should allow researchers to better assess the true risk of fracture in the target population compared with the general population. This should allow more accurate analyses of the value of new interventions in preventing fractures.

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